EXHIBIT 1

serono

September 19, 2002

Dear Doct

At Serono, Inc., we greatly appreciate your ongoing support of our company and our products. Because we value our relationship with you we wanted to be the first to alert you to an issue concerning Serono and Ferring Pharmaceuticals. Unfortunately, Serono has been forced to take legal action against Ferring because we believe that their promotion of Bravelle® (urofollitropin for injection, purified) constitutes a violation of US Patents issued to Serono regarding the use of urinary follicle stimulating hormone (u-FSH). The patents in question cover methods of inducing ovulation and in vitro fertilization with urinary FSH.

As you know, biotechnology companies such as Serono invest a great deal of time and money in the development of new medications. As the pioneer and leader in reproductive care, Serono has been involved in the development of some of the most significant advances in drug therapy for the treatment of infertility. As a result of this leadership, many of our discoveries are protected by patents which enable us to continue to invest resources to identifying and developing advances in reproductive health. We believe strongly that diligently protecting our intellectual property is critical in enabling us to continue to innovate new treatments for patients.

We understand that as a physician, your first concern in any such situation is how it may impact your patients and their care. We at Serono are committed to ensuring that you continue to have access to a complete portfolio of products to treat your patients throughout the fertility cycle.

Thank you for your kind attention and continued support.

Sincerely,

Fereydoun Firouz
Executive Vice President
Reproductive Health, North America
Serono, Inc.

THE ARES-SERONO GROUP

ARGENTINA
AUSTRALIA
AUSTRIA
BELGIUM
BRAZIL
CANADA
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PORTUGAL
SINGAPORE
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USA
VENEZUELA

Serono
PART OF THE ARES-SERONO GROUP
SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

Hi Emyde - Here is a copy of the letter you asked us to send if we could get it! Kathie A

May 16, 2000

Dear Doctor:

We understand that Organon has just announced the launch of its GnRH antagonist. The purpose of this letter is to provide you with some needed clarification regarding certain points made in Organon's announcement letter dated May 16.

- As we have consistently stated, the patent action Serono initiated last year regarding Organon's GnRH antagonist *does not* block Organon's introduction of the product. Until a final determination of what we believe to be a clear infringement of a US patent issued to Serono is made, it is within Organon's discretion to market Antagon™ in any form it chooses.

- We believe that a presentation of Antagon™ as a single product or in combination with any other Organon product equally infringes upon Serono's patent. Organon has initiated arbitration claiming that the sale of their GnRH antagonist is covered under a prior agreement between Organon and Serono's parent companies. We disagree with this claim.

It is unfortunate that Organon has placed you in the uncomfortable position of suggesting you ask Serono for "permission" to purchase Antagon™ as a single product. Please understand why we cannot comply in granting such "permission."

- First, because Antagon™ is Organon's product, current sales of Antagon™ in any form are at Organon's discretion and not ours.

- Second, the only valid "permission" that may be granted for the sale of Antagon™, in our view, is through a license between Serono and Organon. Granting permission outside of such a license would be tantamount to conceding our patent claims against Organon.

- Third, Organon has clearly stated that until a final determination has been made in the pending litigation and ongoing arbitration they have chosen not to offer Antagon™ alone. Therefore, any questions about the decision to sell Antagon™ alone should be directed to Organon representatives.

As of this writing, legal actions between Serono and Organon are ongoing. The goal of our legal challenge is to protect our past and future discovery pipeline. Serono has made many discoveries in the field of infertility and biotechnology. It is only through maintenance and enforcement of patents related to these discoveries that we will be able to assure our continued ability to invent new treatments, new formulations and new products in the future.

We appreciate your continued support. Should you have any questions about the issues discussed in this letter or any other related subject, please contact me or your Serono representative.

Sincerely,

Mike Allen

Mike Allen
Executive Vice President
Reproductive Health Business Unit

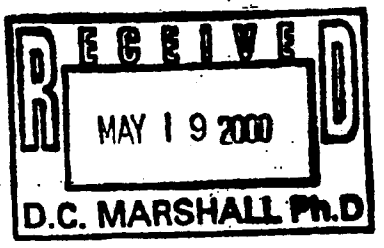


EXHIBIT 2

Just got more convenient.

NEW MULTI-DOSE VIALS

Introducing

GONAL-f

(FOLLITROPIN ALFA FOR INJECTION)

1200 IU Multi-Dose

(delivers 1050 IU)

Convenience.
Comfort.
Satisfaction.

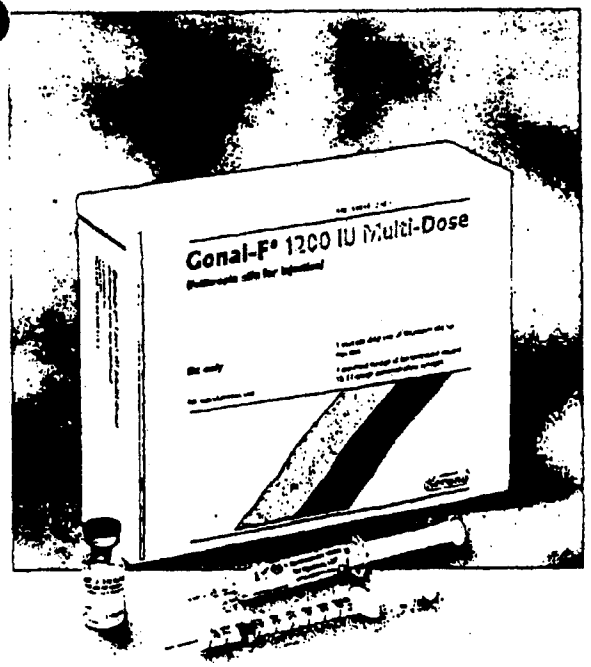
The equivalent of 14 ampules in just 1 vial.

CONVEN

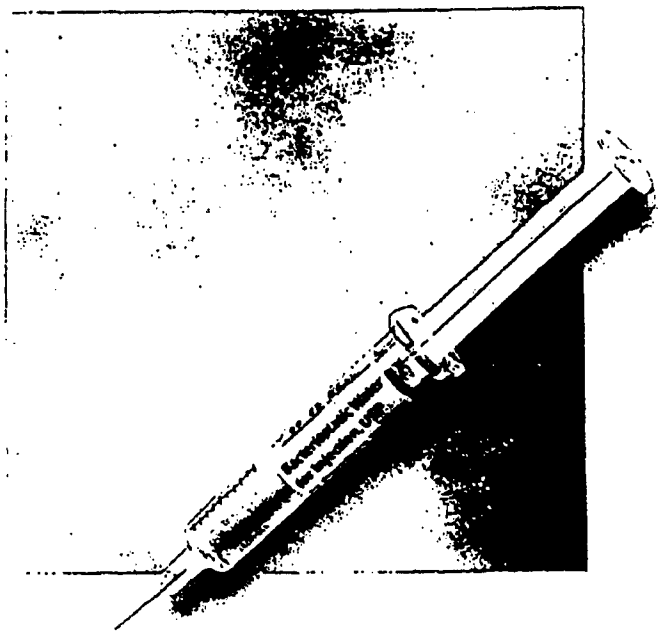
Simplifies dosing and administration for patient convenience

One-step reconstitution replaces time-consuming, daily mixing of multiple ampules or vials

- Each package contains one 1200 IU Multi-Dose vial of Gonal-F® in lyophilized powder form, one 2-mL prefilled syringe of diluent, and fifteen 27-gauge subcutaneous injection syringes
- **Each Multi-Dose vial is filled with 1200 IU to assure delivery of 1050 IU**



- Can be stored at room temperature until reconstitution and then refrigerated for as long as 28 days
- Prefilled syringe of diluent eliminates entire step to maximize convenience—no drawing up of diluent from vial or ampule required



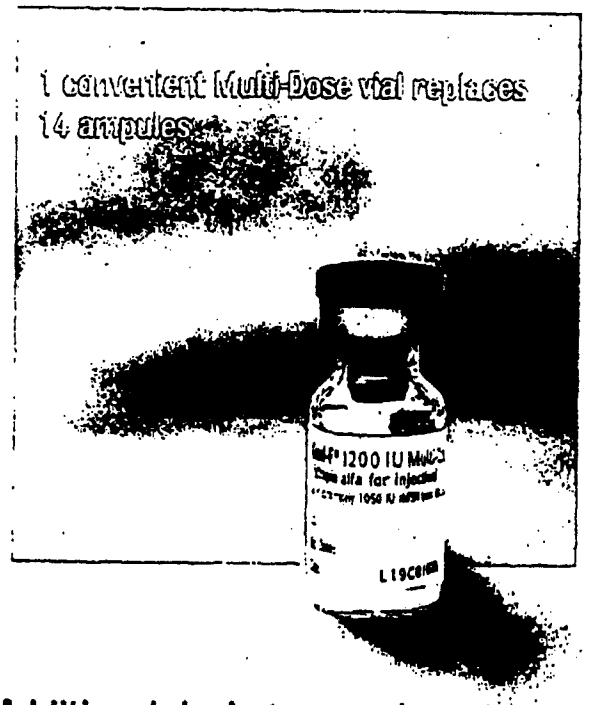
Convenient, Multi-Dose liquid

- Convenient, one-step reconstitution minimizes the potential for mixing errors—and helps reduce associated patient anxiety
- **Once reconstituted, the Multi-Dose liquid formulation provides up to *fourteen 75-IU* equivalents for use over several days**
- A small amount of liquid will remain in the vial; this is normal and expected

Total number of complete doses per vial

Number of doses	Dosage	Total IU*
14	75 IU	1050
7	150 IU	1050
4	225 IU	900
3	300 IU	900
2	450 IU	900

* Maximum deliverable dose from vial is 1050 IU.

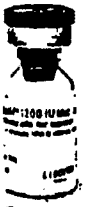


Additional dosing convenience

- A partial dose remaining in a vial can be combined with Gonal-F® from a newly reconstituted vial to make up the balance of your patients' required dose†

† *Please refer your patients to the Patient Instruction Booklet for further instructions.*

Please see full prescribing information provided.



Introducing

GONAL-f®

(FOLLITROPIN ALFA FOR INJECTION)

1200 IU Multi-Dose

Convenience. Comfort. Satisfaction.

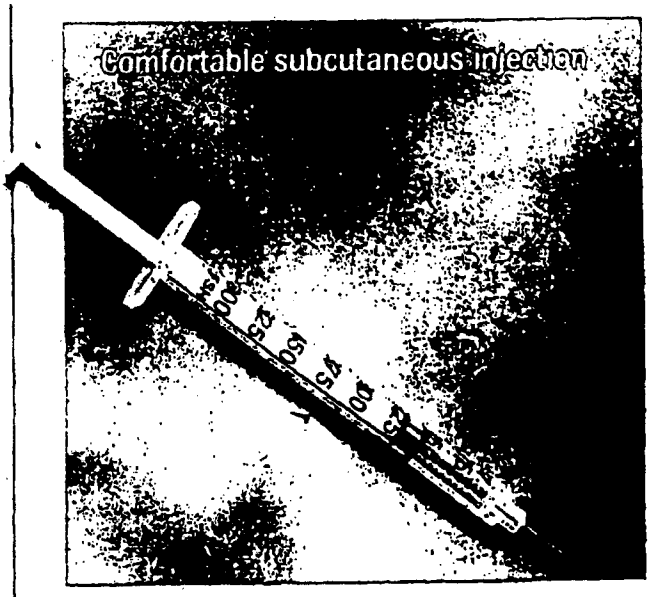
C O A F

Delivers greater patient comfort...

Requires less volume injected per dose compared with other FSH formulations

Lower volume injections are:

- Quicker
- More comfortable[1]
- Patient friendly

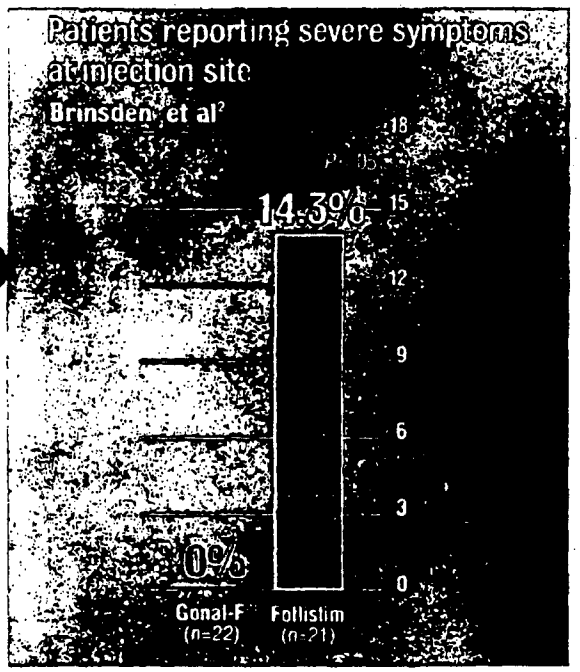


O R T

Gonal-F®: Highly effective r-hFSH therapy doesn't have to sting

Gonal-F® was significantly better tolerated at the injection site than Follistim®[2]*

- No patient receiving Gonal-F® experienced a severe reaction[2†]



P≤.05 for comparison of all local skin reactions at injection site regardless of severity.

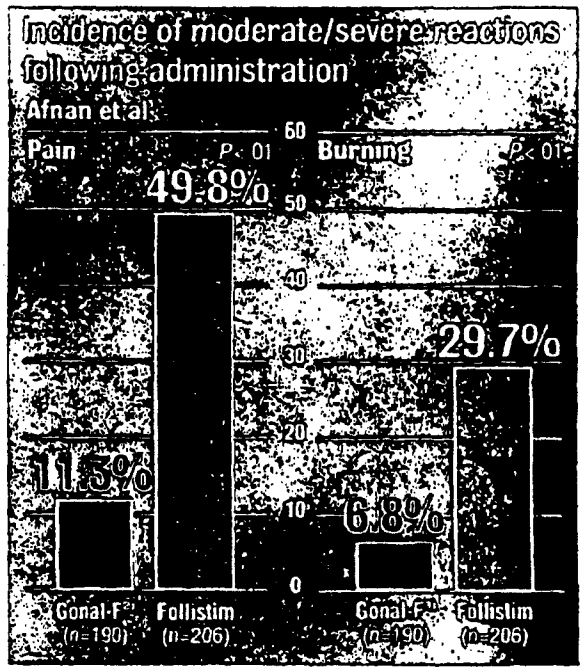
* Follistim was reconstituted using 0.45% sodium chloride diluent.

† Itching, bruising, and pain.

‡ Studies utilized 75-IU ampules.

Follistim® (US) and Puregon® (International) are registered trademarks of Organon Inc. for follitropin beta for injection. Studies utilized non-US strengths—50 IU and 100 IU vials.

Pain and burning were reported by patients more than four times more frequently following 150-IU injections of Follistim vs Gonal-F®[3]



Introducing

GONAL-f®
(FOLLITROPIN ALFA FOR INJECTION)
1200 IU Multi-Dose

Convenience. Comfort. Satisfaction.

Please see full prescribing information provided.

S A T I S F

Gonal-F® 1200 IU Multi-Dose provides dosing flexibility that's easier for patients

Flexible dosing from one convenient Multi-Dose vial simplifies dosing and helps minimize patient confusion

- Custom syringe graduated in 37.5-IU increments for easy, accurate dosing and administration
- Syringe allows for easy withdrawal of exact dose in IU
- Easy for patients to comply with dosing adjustments

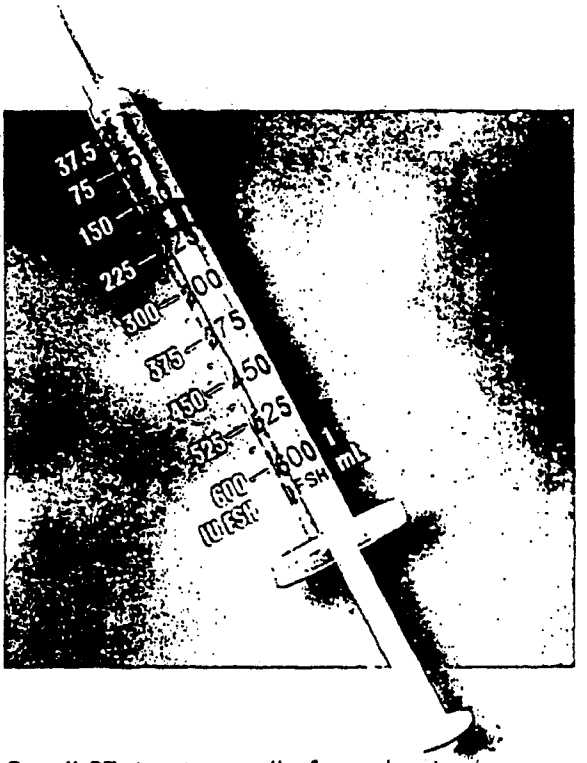
Required dose	Ampule equivalent
75 IU	1
150 IU	2
225 IU	3
300 IU	4
375 IU	5
450 IU	6

Multi-Dose vial equivalent

1 Multi-Dose vial = up to 14 ampules

2 Multi-Dose vials = up to 28 ampules

3 Multi-Dose vials = up to 42 ampules



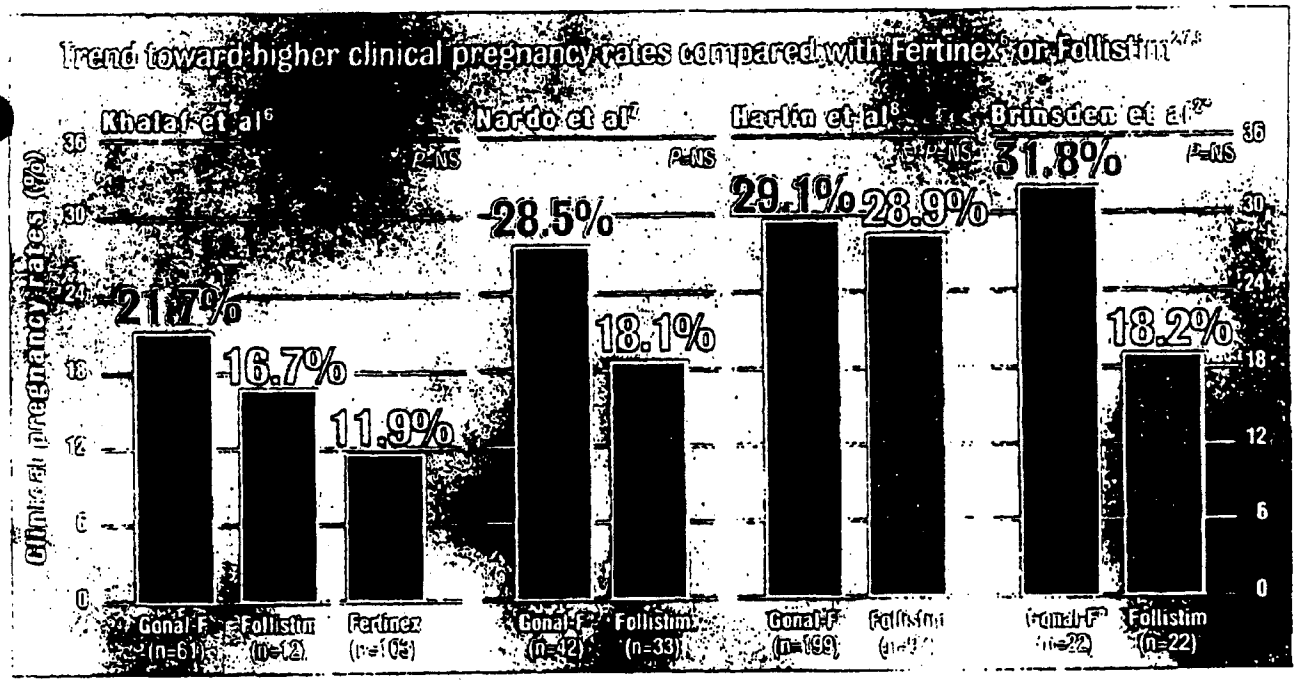
- Small 27-gauge needle for subcutaneous administration

A C T I O N

Rely on unsurpassed efficacy of Gonal-F® to provide your patients with high-quality embryos[4-6] and successful clinical pregnancies[2,6-8]

Significantly more high-quality embryos compared with Follistim[4,5] or Fertinex®[6]

Endpoint	Study	*P* value in favor of Gonal-F®
% of high-quality embryos	Phillips et al[4]	$P \leq .05$
Mean # of high-quality embryos	von Düring et al[5]	$P < .05$
Mean # of high-quality embryos	Khalaf et al[6]	$P < .001$, vs Fertinex $P < .30$, Follistim vs Fertinex



Introducing

GONAL-f®
(FOLLITROPIN ALFA FOR INJECTION)
1200 IU Multi-Dose
Convenience. Comfort. Satisfaction.

Diagnosis of clinical pregnancy was confirmed by serial serum of β-hCG concentrations and ultrasound visualization of fetal sac.

Follistim® (US) and Puregon® (International) are registered trademarks of Organon Inc. for follitropin beta for injection. Studies utilized non-US strengths—50 IU and 100 IU vials.

Fertinex® (urofollitropin for injection, purified).

Please see full prescribing information provided.

Our family of patient-friendly products

For the patient

- Convenience — portable and less preparation per injection
- Comfort — better tolerated than Follistim[2,3] and lower volume injections than single dose
- Satisfaction — injection syringe graduated in IU for easier precise dosing

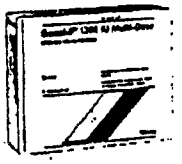
For the physician and nurse

- Convenience — simplified dosing is easy to understand and syringes are provided with Gonal-F® 1200 IU Multi-Dose
- Comfort — fewer patient complaints about injection site discomfort
- Satisfaction — trend toward higher clinical pregnancy rates with Gonal-F® vs Follistim[2,7,8] or u-FSH[9]

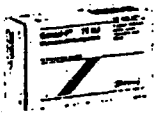
Safe and well-tolerated r-hFSH therapy

Important safety information

Gonal-F® (follitropin alfa for injection) should only be used by physicians who are thoroughly familiar with infertility problems and their management. Gonal-F® is a potent gonadotropin capable of causing ovarian hyperstimulation syndrome (OHSS) with or without pulmonary vascular complications, which can be fatal. The incidence of severe OHSS is less than 0.5% in patients in controlled clinical trials. The incidence of multiple births was 14% in OI and 33% in ART. The most common side effects are headache, ovarian cysts, nausea, and upper respiratory tract infections in women; and acne, breast pain and enlargement, and fatigue in men. Infrequent reports of benign and malignant ovarian neoplasms have been reported in women undergoing multiple infertility regimens; however, a causal relationship has not been established.

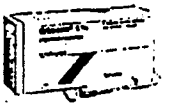


NEW Gonal-F® 1200 IU Multi-Dose
(FOLLITROPIN ALFA FOR INJECTION)

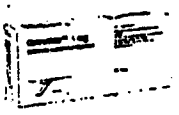


Gonal-F® 75 IU
(FOLLITROPIN ALFA FOR INJECTION)

Gonal-F® 37.5 IU
(FOLLITROPIN ALFA FOR INJECTION)

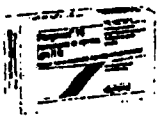


Crinone® 4% and 8%
(PROGESTERONE GEL)

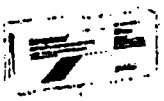


Cetrotide™ 0.25 mg and 3 mg
(CETRORELIX ACETATE FOR INJECTION)

Ovidrel®
(CHORIOGONADOTROPIN ALFA FOR INJECTION)



Pergonal®
(MENOTROPINS FOR INJECTION, USP)



Serophene®
(CLOMIPHENE CITRATE TABLETS, USP)

Please see full prescribing information provided.

References: 1. Jorgensen JT, Ramsing J, Rasmussen M, et al. Pain assessment of subcutaneous injections. *Ann Pharmacother.* 1998;30:729-732. 2. Brinsden P, Akagbosu F, Gibbons LM, et al. A comparison of the efficacy and tolerability of two recombinant human follicle-stimulating hormone preparations in patients undergoing in vitro fertilization-embryo transfer. *Fertil Steril.* 2000;73:114-118. 3. Athen MA, Kennedick A. Recombinant gonadotropins: is there a difference in the tolerability of these products? Presented at the British Fertility Society Annual General Meeting, 1998. 4. Phillips E, Page M, Fleming SD. A prospective comparison of two different recombinant FSH preparations. *ART in the New Millennium: Progress in Practice.* The 11th World Congress on In Vitro Fertilization and Human Reproductive Genetics. May 10, 1999; Sydney, Australia. Abstract. 5. von Düring V, Kahn JA, Sunde A, et al. Results of a prospective, randomized study comparing two r-FSH preparations (Gonal-F®, Puregon®) in IVF and ICSI treatments. *ART in the New Millennium: Progress in Practice.* The 11th World Congress on In Vitro Fertilization and Human Reproductive Genetics. May 10, 1999; Sydney, Australia. Abstract. 6. Khalaf Y, Anderson H, Taylor A, et al. Comparative clinical evaluation of recombinant and urinary human follicle stimulating hormone in assisted reproduction. *Reprod Technol.* 2000;10:2-6. 7. Nardo LG, Bellanca SA, Messina K, et al. Efficacy of recombinant follicle stimulating hormone versus urinary follicle stimulating hormone in in-vitro fertilization: a prospective, randomized, assessor-blind study. *Ital J Gynaecol Obstet.* 2000;2:49-53. 8. Harlin J, Csemiczky G, Wramsby H, et al. Recombinant follicle stimulating hormone in in-vitro fertilization treatment — clinical experience with follitropin alfa and follitropin beta. *Hum Reprod.* 2000;15:239-244. 9. Daya S, Gunby J. Recombinant versus urinary follicle stimulating hormone for ovarian stimulation in assisted reproduction. *Hum Reprod.* 1999;14:2207-2215.

EXHIBIT 3

FERRING
PHARMACEUTICALS

June 5, 2002

Mr. Thomas W. Abrams, R.Ph., MBA,
Director, Division of Drug Marketing, Advertising and Communications
HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Misleading Promotion of Gonal-F (Follitropin Alfa for Injection) and public health issues

Dear Mr. Abrams:

In preparation for the launch of one of our products we reviewed the current promotional brochure for Gonal-F® (Follitropin Alfa for Injection) marketed by Serono Laboratories (see Tab 1). We believe that this brochure contains several false and misleading claims. Many of these claims lack substantiation misstate study findings and misuse statistical operations and graphics to create false impressions about the safety and effectiveness of Gonal-F, potentially causing public health issues.

Certain of these claims are directly contradictory to the FDA Statistical Officer's Review of the product (see Tab 2). These false and misleading claims not only create an unfair marketing environment, but they threaten the public health environment as physicians may be misled into believing that this product is safer and more efficacious than existing or newly introduced products. We request that DDMAC take action to halt this and similar violative promotions. In the sections below we review the specific false and misleading promotional claims for Gonal-F that are contained in this promotional brochure.

Overall Claims of Efficacy

On page 7 of the enclosed brochure Serono asserts that Gonal-F increases patient/physician/nurse satisfaction by having greater efficacy than similar products. At various points on page 7 the efficacy of Gonal-F is discussed. The number of **"high quality embryos"** is described as **"significantly more"** than competing products. However, there is no definition of **"high quality embryos"**, a highly subjective term. In addition, the first two references quoted as showing significant differences are abstracts so that the true data cannot be evaluated, nor can the nature of the studies, their conduct, or the statistical analyses. To augment this claim of superior efficacy the brochure presents a series of charts that display the results of four studies of clinical pregnancy rates. In each

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900, Telefax: (914) 631-1992

FERRING

chart the clinical pregnancy rates for Gonal-F are shown as higher than the other products. The headline for the chart states that there is a **"Trend toward higher clinical pregnancy rates compared with..."** competing products. The impression conveyed by these statements is that Gonal-F is superior in efficacy to the competing products. However, in small type it is noted that none of the differences are statistically significant. The use of a bar chart with an upper limit of 36% is also misleading as it serves to exaggerate the differences among the products. Use of the term "trend" falsely implies that there is a statistical difference of at least $p < 0.10$ among the groups.

This graphic display and use of the term "trend" are misleading. The suggestion of Gonal-F superiority is directly denied by the studies we could find. We located two of the four studies cited in the graph. In the Harlin study (see Tab 3) the difference between pregnancy rates is less than 1% and the authors concluded that there was no difference between the drugs. Although there was about a 14% difference among the drugs in the Brisden et al. study (see Tab 4), the difference was not statistically significant ($p= 0.30$). Here too, the authors concluded that *"...demonstrated their equivalent efficacy, with no statistically significant differences in any of the measured outcomes."* We were unable to locate the other studies cited on this page and could not verify if the claims presented were truthful. However, we believe that the overall impression produced by these claims is clinical superiority. Based on the studies we could find, and the impression left by the chart, we believe that this implied claim is not supported.

The presentation of these data to suggest greater efficacy for Gonal-F is directly contradicted by the FDA's Statistical Officer's Review of the product, in which he noted that Gonal-F appears inferior to the comparator, Metrodin. Specifically, the Statistical Officer stated:

1. *"A significant treatment difference was detected in favor of Metrodin over Gonal-F with regard to the primary efficacy parameter."* (Tab 2)
2. *"...it is statistically conceivable that a clinically important difference exists in favor of Metrodin over Gonal-F."* (Tab 2)
3. *"A numerical superiority was also detected in favor of Metrodin over Gonal-F with regard to the sponsor's 'relevant' secondary efficacy parameters."* (Tabs 2 and 5)

The data referenced do not refute the Statistical Officer's Review and we therefore believe that the presentation of the data and the claim of **"...unsurpassed efficacy"** are lacking in fair balance and are false and misleading.

Overall Claims of Convenience, Comfort and Satisfaction

While claims of convenience may be substantiated by reference to a particular dosage form, recent letters issued by DDMAC make it clear that claims of "comfort" and "satisfaction" need to be based on substantial evidence derived from patient reported outcomes data. The Gonal-F claims clearly lack this level of support. Furthermore, studies used to support the NDA for Gonal-F demonstrate significant injection site

problems (relevant to "comfort") compared to alternative treatments. For example, the Medical Officer (see Tab 5) stated in his review *"...the severity of redness developed as a consequence of treatment injections was significantly greater with Gonal-F than with Metrodin."* Failure to report these material facts violates FDA regulations.

Comfort Claims

On page 4 the brochure states that Gonal-F **"Delivers greater patient comfort..."** It is important to note that the original NDA submission for Gonal-F contained a comparison of injection site tolerability. Gonal-F was found to produce significantly more redness than its comparator (Urofolitropin). Both the Statistical and Medical Officers' reviews of this drug (see Tabs 2 and 5) note this difference. The Statistical Officer stated that *"In addition, local injection reactions exhibited by study patients indicated that such reactions were more severe in the Gonal-F treatment group with statistical significance (p=0.043) being attained with regard to the severity of redness."* The existence of data in the Gonal-F NDA showing that Gonal-F caused significantly more redness than Urofolitropin is a material fact that is not disclosed in the brochure. This information is necessary for a reader to fully understand and evaluate the comfort claims in the brochure and the failure to mention of these data appears to be lacking in fair balance as well as false and misleading.

Satisfaction Claims

Claims for satisfaction are based on two lines of presented evidence (see pages 6 and 7 of the brochure). First, it is strongly implied that Gonal-F increases patient satisfaction because of dosing flexibility. While such dosing may increase convenience for patients, the brochure also claims that Gonal-F dosing will **"minimize patient confusion"** and make it **"Easy for patients to comply with dosing adjustments"** (see page 6). There are no data to support these outcome claims.

Importantly, the implied claim that Gonal-F is superior in satisfaction is totally unsubstantiated. There are no measures of patient or health professional satisfaction. The back page of the brochure reinforces the false and misleading information by again asserting comfort and satisfaction claims.

Request for FDA Action

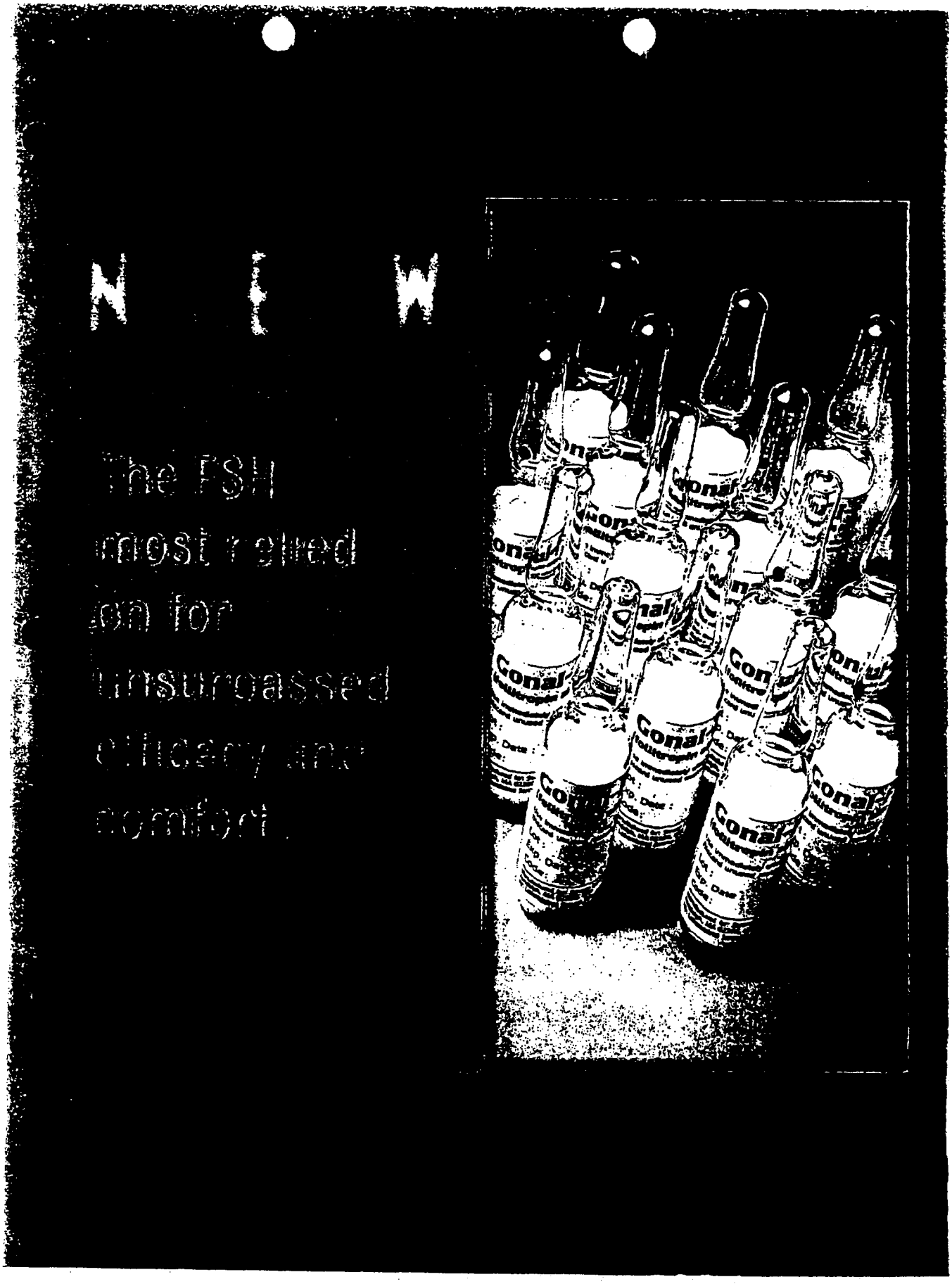
We request that you take action against Serono's dissemination of false and misleading material. The flagrant misuse of statistical and graphic representation of data and failure to disclose contradictory data that appear in the original NDA is clearly prohibited by FDA regulations. The misuse of such data to make false and misleading comparative claims presents a serious pubic health concern, as health care providers may rely on such inaccurate information to incorrectly believe that Gonal-F is a superior product.

We feel very strongly that these are important issues and that these and similar issues are prevalent in much of Serono's promotional materiel for Gonal-F. We look forward to your review of this brochure. If we can be of any further service, please contact Dr. Michael Bernhard at (914) 333-8958. We would appreciate being informed of any action you take in regards to this matter.

Sincerely,

MBernhard

Michael I. Bernhard, Ph.D.
Senior Director, Regulatory Affairs


N E W
The FSH
most trusted
on for
unsurpassed
efficacy and
comfort.
Conal

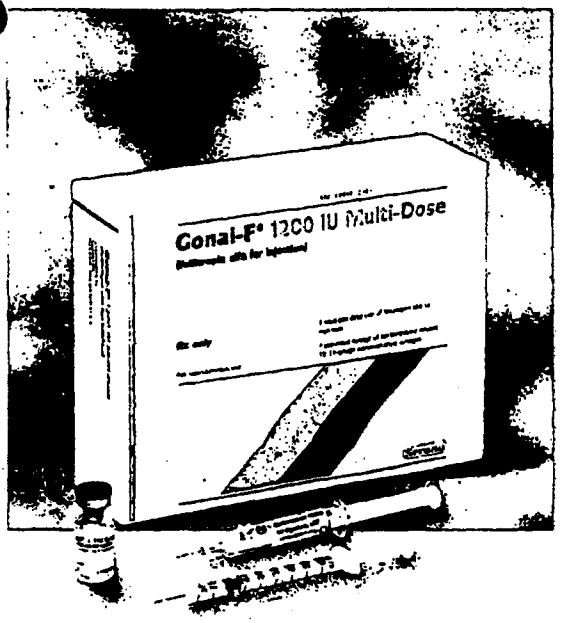

Just got more convenient.
NEW MULTI-DOSE VIALS
Introducing
GONAL-f
(FOLLITROPIN ALFA FOR INJECTION)
1200 IU Multi-Dose
(delivers 1050 IU)
Convenience.
Comfort.
Satisfaction.
the equivalent of 14 ampules in just 1 vial.

CONVEN

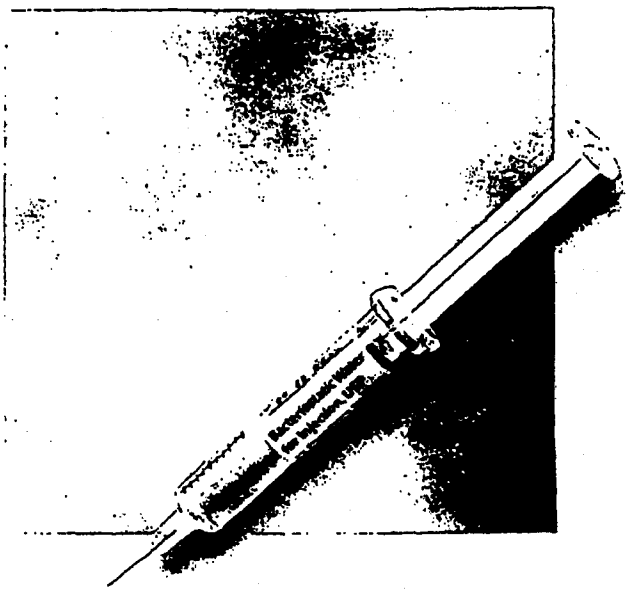
Simplifies dosing and administration for patient convenience

One-step reconstitution replaces time-consuming, daily mixing of multiple ampules or vials

- Each package contains one 1200 IU Multi-Dose vial of Gonal-F® in lyophilized powder form, one 2-mL prefilled syringe of diluent, and fifteen 27-gauge subcutaneous injection syringes
- **Each Multi-Dose vial is filled with 1200 IU to assure delivery of 1050 IU**



- Can be stored at room temperature until reconstitution and then refrigerated for as long as 28 days
- Prefilled syringe of diluent eliminates entire step to maximize convenience—no drawing up of diluent from vial or ampule required



I E N C E

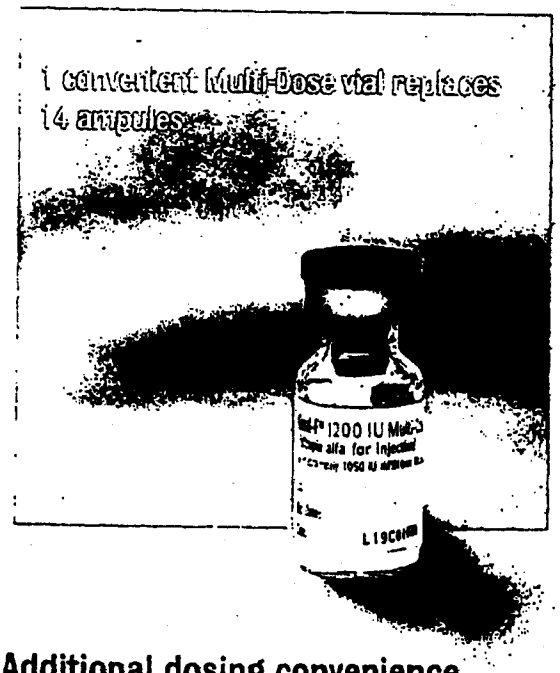
Convenient, Multi-Dose liquid

- Convenient, one-step reconstitution minimizes the potential for mixing errors—and helps reduce associated patient anxiety
- **Once reconstituted, the Multi-Dose liquid formulation provides up to *fourteen 75-IU* equivalents for use over several days**
- A small amount of liquid will remain in the vial; this is normal and expected

Total number of complete doses per vial

Number of doses	Dosage	Total IU*
14	75 IU	1050
7	150 IU	1050
4	225 IU	900
3	300 IU	900
2	450 IU	900

* Maximum deliverable dose from vial is 1050 IU.

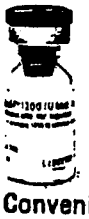


Additional dosing convenience

- A partial dose remaining in a vial can be combined with Gonal-F® from a newly reconstituted vial to make up the balance of your patients' required dose†

† *Please refer your patients to the Patient Instruction Booklet for further instructions.*

Please see full prescribing information provided.



Introducing

GONAL-f®

(FOLLITROPIN ALFA FOR INJECTION)

1200 IU Multi-Dose

Convenience. Comfort. Satisfaction.

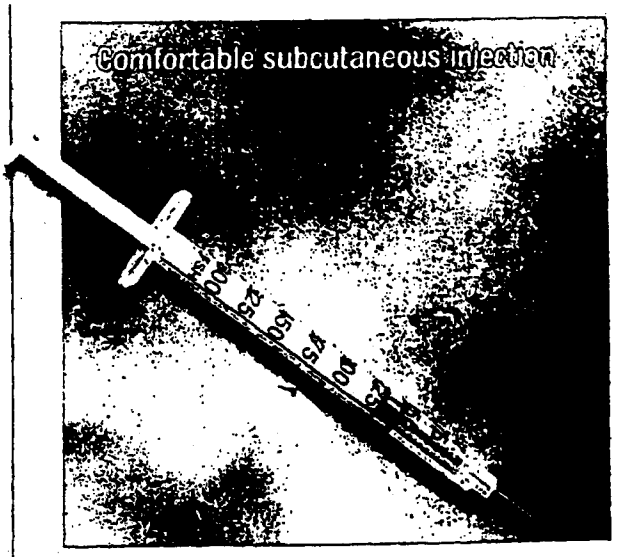
C O M F

Delivers greater patient comfort...

Requires less volume injected per dose compared with other FSH formulations

Lower volume injections are:

- Quicker
- More comfortable[1]
- Patient friendly

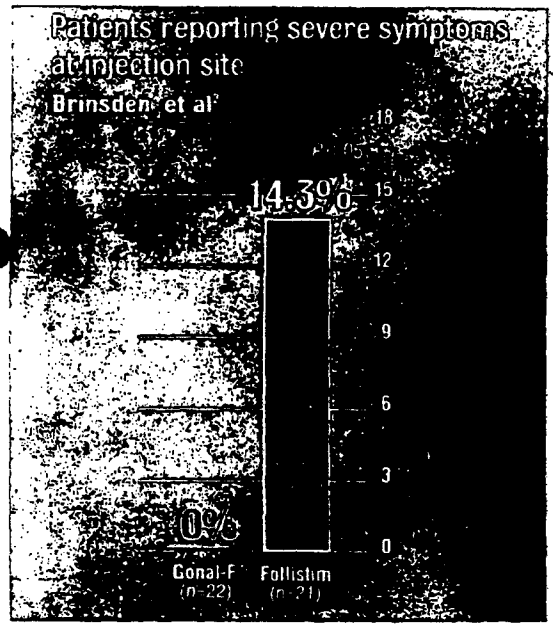


O R T

Gonal-F®: Highly effective r-hFSH therapy doesn't have to sting

Gonal-F® was significantly better tolerated at the injection site than Follistim®2*

- No patient receiving Gonal-F® experienced a severe reaction2†



P≤.05 for comparison of all local skin reactions at injection site regardless of severity.

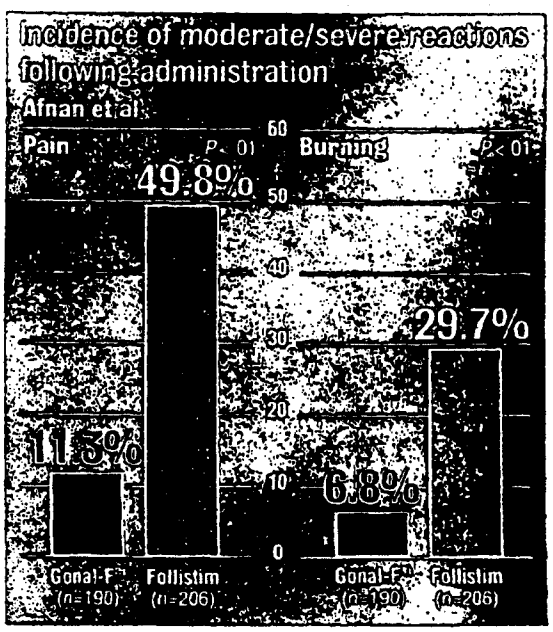
* Follistim was reconstituted using 0.45% sodium chloride diluent.

† Itching, bruising, and pain.

‡ Studies utilized 75-IU ampules.

Follistim® (US) and Puregon® (International) are registered trademarks of Organon Inc. for follitropin beta for injection. Studies utilized non-US strengths—50 IU and 100 IU vials.

Pain and burning were reported by patients more than four times more frequently following 150-IU injections of Follistim vs Gonal-F®3



Introducing

GONAL-f®
(FOLLITROPIN ALFA FOR INJECTION)
1200 IU Multi-Dose

Convenience. Comfort. Satisfaction.

Please see full prescribing information provided.

5

S A T I S F

Gonal-F® 1200 IU Multi-Dose provides dosing flexibility that's easier for patients

Flexible dosing from one convenient Multi-Dose vial simplifies dosing and helps minimize patient confusion

- Custom syringe graduated in 37.5-IU increments for easy, accurate dosing and administration
- Syringe allows for easy withdrawal of exact dose in IU
- Easy for patients to comply with dosing adjustments

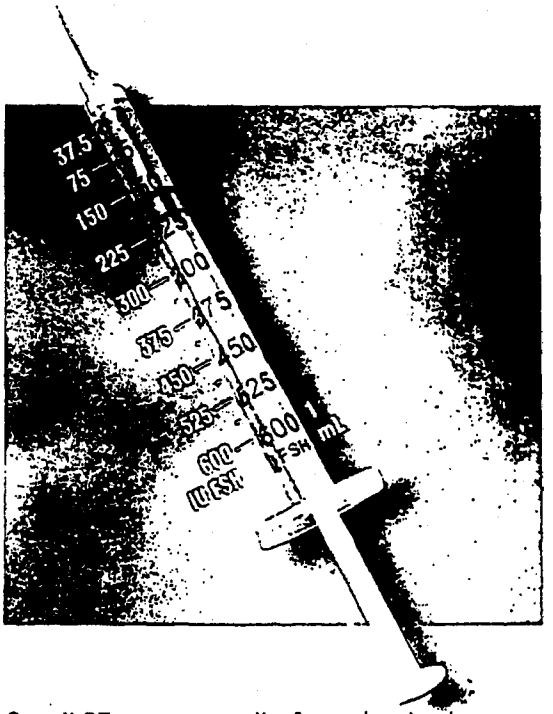
Required dose	Ampule equivalent
75 IU	1
150 IU	2
225 IU	3
300 IU	4
375 IU	5
450 IU	6

Multi-Dose vial equivalent

1 Multi-Dose vial = up to 14 ampules

2 Multi-Dose vials = up to 28 ampules

3 Multi-Dose vials = up to 42 ampules



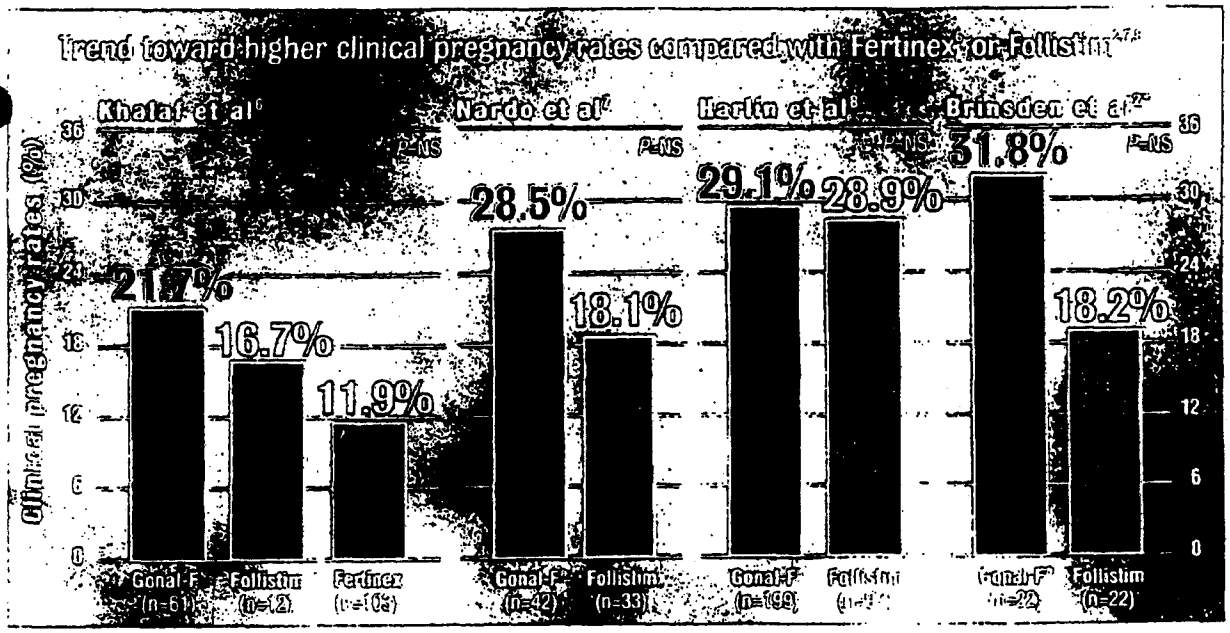
- Small 27-gauge needle for subcutaneous administration

ACTION

Rely on unsurpassed efficacy of Gonal-F® to provide your patients with high-quality embryos[4-6] and successful clinical pregnancies[2,6-8]

Significantly more high-quality embryos compared with Follistim[4,5] or Fertinex®[6]

Endpoint	Study	*P* value in favor of Gonal-F®
% of high-quality embryos	Phillips et al[4]	$P \leq .05$
Mean # of high-quality embryos	von Düring et al[5]	$P < .05$
Mean # of high-quality embryos	Khalaf et al[6]	$P < .001$, vs Fertinex $P < .30$, Follistim vs Fertinex



Introducing

GONAL-f®
(FOLLITROPIN ALFA FOR INJECTION)
1200 IU Multi-Dose
Convenience. Comfort. Satisfaction.

Diagnosis of clinical pregnancy was confirmed by serial serum of β-hCG concentrations and ultrasound visualization of fetal sac.

Follistim® (US) and Puregon® (International) are registered trademarks of Organon Inc. for follitropin beta for injection. Studies utilized non-US strengths—50 IU and 100 IU vials.

Fertinex® (urofollitropin for injection, purified).

Please see full prescribing information provided.

Our family of patient-friendly products

For the patient

- Convenience — portable and less preparation per injection
- Comfort — better tolerated than Follistim[2,3] and lower volume injections than single dose
- Satisfaction — injection syringe graduated in IU for easier precise dosing

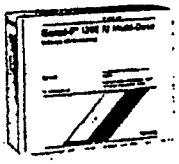
For the physician and nurse

- Convenience — simplified dosing is easy to understand and syringes are provided with Gonal-F® 1200 IU Multi-Dose
- Comfort — fewer patient complaints about injection site discomfort
- Satisfaction — trend toward higher clinical pregnancy rates with Gonal-F® vs Follistim[2,7,8] or u-FSH[9]

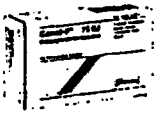
Safe and well-tolerated r-hFSH therapy

Important safety information

Gonal-F® (follitropin alfa for injection) should only be used by physicians who are thoroughly familiar with infertility problems and their management. Gonal-F® is a potent gonadotropin capable of causing ovarian hyperstimulation syndrome (OHSS) with or without pulmonary vascular complications, which can be fatal. The incidence of severe OHSS is less than 0.5% in patients in controlled clinical trials. The incidence of multiple births was 14% in OI and 33% in ART. The most common side effects are headache, ovarian cysts, nausea, and upper respiratory tract infections in women; and acne, breast pain and enlargement, and fatigue in men. Infrequent reports of benign and malignant ovarian neoplasms have been reported in women undergoing multiple infertility regimens; however, a causal relationship has not been established.

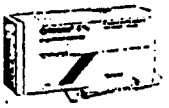


NEW Gonal-F® 1200 IU Multi-Dose
(FOLLITROPIN ALFA FOR INJECTION)

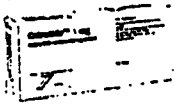


Gonal-F® 75 IU
(FOLLITROPIN ALFA FOR INJECTION)

Gonal-F® 37.5 IU
(FOLLITROPIN ALFA FOR INJECTION)



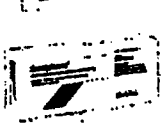
Crinone® 4% and 8%
(PROGESTERONE GEL)



Cetrotide™ 0.25 mg and 3 mg
(CETRORELIX ACETATE FOR INJECTION)

Ovidrel®
(CHORIOGONADOTROPIN ALFA FOR INJECTION)

Pergonal®
(MENOTROPINS FOR INJECTION, USP)



Serophene®
(CLOMIPHENE CITRATE TABLETS, USP)

Please see full prescribing information provided.

References: 1. Jorgensen JT, Romsing J, Rasmussen M, et al. Pain assessment of subcutaneous injections. *Ann Pharmacother.* 1996;30:729-732. 2. Brinsden P, Akagbosu F, Gibbons LM, et al. A comparison of the efficacy and tolerability of two recombinant human follicle-stimulating hormone preparations in patients undergoing in vitro fertilization-embryo transfer. *Fertil Steril.* 2000;73:114-118. 3. Afnan MA, Kennedick A. Recombinant gonadotropins: is there a difference in the tolerability of these products? Presented at the British Fertility Society Annual General Meeting, 1998. 4. Phillips E, Page M, Fleming SD. A prospective comparison of two different recombinant FSH preparations. *ART in the New Millennium: Progress in Practice.* The 11th World Congress on In Vitro Fertilization and Human Reproductive Genetics. May 10, 1999; Sydney, Australia. Abstract. 5. von Düring V, Kahn JA, Sunde A, et al. Results of a prospective, randomized study comparing two r-FSH preparations (Gonal-F®, Puregon®) in IVF and ICSI treatments. *ART in the New Millennium: Progress in Practice.* The 11th World Congress on In Vitro Fertilization and Human Reproductive Genetics. May 10, 1999; Sydney, Australia. Abstract. 6. Khalaf Y, Anderson H, Taylor A, et al. Comparative clinical evaluation of recombinant and urinary human follicle stimulating hormone in assisted reproduction. *Reprod Technol.* 2000;10:2-6. 7. Nardo LG, Bellance SA, Messina K, et al. Efficacy of recombinant follicle stimulating hormone versus urinary follicle stimulating hormone in in-vitro fertilization: a prospective, randomized, assessor-blind study. *Ital J Gynaecol Obstet.* 2000;2:49-53. 8. Harlin J, Csemiczky G, Wramsby H, et al. Recombinant follicle stimulating hormone in in-vitro fertilization treatment — clinical experience with follitropin alfa and follitropin beta. *Hum Reprod.* 2000;15:239-244. 9. Daya S, Gunby J. Recombinant versus urinary follicle stimulating hormone for ovarian stimulation in assisted reproduction. *Hum Reprod.* 1999;14:2207-2215.

JUN 30 1994

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-378/Drug Class 3S

APPLICANT: Serono Laboratories, Inc.

NAME OF DRUG: Gonal-F (recombinant human follicle stimulating hormone for injection)

INDICATION: Stimulation of multiple follicular development in female patients undergoing in vitro fertilization and embryo transfer (IVF-ET)

DOCUMENTS REVIEWED: Volumes 1.1, 1.56-1.69 of NDA 20-378 dated September 15, 1993 and Volume 1 of NDA 20-378 dated May 20, 1994.

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Ridgely C. Bennett, M.D. (HFD-510)

RELEVANT ISSUES DISCUSSED IN THIS REVIEW:

1. A significant treatment difference was detected in favor of Metrodin over Gonal-F with regard to the primary efficacy parameter.

2. The resulting 95% primary efficacy parameter treatment difference confidence interval indicates that it is statistically conceivable that a clinically important difference exists in favor of Metrodin over Gonal-F.

3. The severity of redness developed as a consequence of treatment injections was significantly greater with Gonal-F than with Metrodin.

The sponsor has submitted the results of the randomized multi-center (9 European clinical centers) open Study GF5503 which was conducted to compare the efficacy and safety of Gonal-F administered subcutaneously with Metrodin administered intramuscularly, for stimulating multiple follicular development in women undergoing in vitro fertilization and embryo transfer.

KEY WORDS: clinical assessment, confidence interval, embryo transfer, injections, in vitro fertilization, matured follicles, Metrodin, oocytes, recombinant human follicle stimulating hormone, redness

Subsequent to randomization to Gonal-F or Metrodin, all patients commenced treatment (at mid-luteal phase of a spontaneous cycle) with a G_nRH agonist (buserelin 20 mcg daily administered subcutaneously) to induce pituitary gonadotrope cell densensitization to control endogenous secretion of LH during the superovulation treatment. On days 3 to 5 of subsequent menstruation, patients commenced randomized treatment at an initial dose of 225 IU FSH/day.

Dose adaptation was allowed if necessary after fives days of stimulation based upon the ovarian response to FSH therapy as assessed by serum E_2 levels and follicle growth by ultrasound. Each patient was to undergo only one treatment cycle and would not receive more than 450 IU FSH daily or 6,000 IU FSH during the treatment cycle.

Final follicular maturation was induced by administration of human chorionic gunadotropin (hCG) when the follicular response was judged to be adequate. Oocytes were retrieved, fertilized in vitro and some embryos replaced. Patients were then followed up and the outcome (pregnancy or menstruation) was recorded.

The primary efficacy parameter was the number of pre-ovulatory follicles (excluding cysts) definded as those which were (matured) at least 14 mm in diameter on the day of hCG administration. Secondary efficacy parameters included the number of follicles recruited, defined as follicles greater than 10mm in diameter, the number of oocytes recovered, the number of oocytes fertilized and the number of cleaved embryos.

The sponsor's claim that recombinant human FSH (Gonal-F) is as safe and effective as urinary FSH (Metrodin) for the stimulation of follicular development is addressed below.

Reviewer's Comments on Study GF5503

A total of 124 patients (61 Gonal-F, 63 Metrodin) were randomized to receive open treatment. Four of these patients (2 Gonal-F, 2 Metrodin) left the study prior to the completion of treatment. An additional 17 patients (8 Gonal-F, 9 Metrodin) left the study after completion of FSH treatment but before embryo transfer.

The sponsor conducted all patient and evaluable patient analyses. The all patient analyses included 123 patients as one patient who inadvertently received both treatments was excluded from these analyses. The evaluable patient analyses included only 115 patients (58 Gonal-F, 57 Metrodin) as an additional 8 patients were excluded due to protocol violations.

The remainder of this review will focus on the sponsor's all patient analyses as the all patient and evaluable patient results were similar.

Table 1 displays the results of the sponsor's primary efficacy parameter analysis. In examining this table, one notes that a significantly (p=.0365) greater number of follicles of at least 14mm in diameter existed in the Metrodin group in comparison to the Gonal-F group on the day of hCG administration. This result was consistent across centers as Metrodin numerically outperformed Gonal-F in each center.

It should also be noted that the study was designed to have adequate power (80%) to detect a treatment difference of 2 matured follicles. In fact, the sponsor stated that a between-treatment difference of 2 follicles or less was not considered clinically important. However, in examining the total 95% follicle difference confidence interval displayed in Table 1 of (.09, 2.61), it is apparent that values greater than 2 are included in this interval. Consequently, it is statistically conceivable that there is a clinically important treatment difference in favor of Metrodin over Gonal-F with regard to the designated primary efficacy parameter. The ramification of this finding needs to be addressed by the clinical reviewer.

Table 2 displays the results of the sponsor's analyses conducted with regard to "relevant secondary efficacy parameters", as designated by the sponsor. In examining this table, one notes that significant differences were not detected with regard to these secondary parameters. However, the Metrodin treatment group numerically outperformed the Gonal-F treatment group in each case. The clinical reviewer should examine the resulting 95% confidence intervals also displayed in Table 2 in order to properly interpret these nonsignificant findings.

Excluding local reactions to injections, 30 patients (11 Gonal-F, 19 Metrodin, p=.06) experienced at least one adverse event during treatment. The most frequent adverse event was ovarian cyst (3 Gonal-F, 8 Metrodin, p=.13).

Local tolerance to treatment was assessed by asking patients to record on a card, daily, any injection site reactions they experienced after each injection. Five symptoms were recorded: itching, swelling, redness, bruising, and pain using a scale of none, mild, moderate, or severe.

The local tolerance analyses conducted by the sponsor was on a per patient basis in which the most severe reaction for each symptom was recorded for each patient. The results of these analyses are displayed in Table 3. In examining this table, one notes that the severity of redness was significantly (p=.043) greater with Gonal-F than with Metrodin. There were no significant differences detected with respect to the remaining symptoms although the results were numerically in favor of Metrodin over Gonal-F in each case.

Reviewer's Concluding Comments (may be conveyed to the sponsor)

Study GF5503 was adequately powered to detect a treatment difference of 2 matured follicles where a difference of 2 follicles or less was not considered clinically important.

The sponsor's all patient primary efficacy parameter (matured follicles) analysis detected a significant difference (p=.0365) in favor of Metrodin over Gonal-F. In fact, the 95% between-treatment (Metrodin minus Gonal-F) confidence interval (.09, 2.61) contains values in excess of the aforementioned critical threshold value of 2 matured follicles. Consequently, by the sponsor's definition, it is statistically conceivable that a clinically important treatment difference with regard to matured follicles exists in favor of Metrodin over Gonal-F.

A numerical superiority was also detected in favor of Metrodin over Gonal-F with regard to the sponsor's "relevant" secondary efficacy parameters.

In addition, local injection reactions exhibited by study patients indicated that such reactions were more severe in the Gonal-F treatment group with statistical significance (p=.043) being attained with regard to the severity of redness.

Consequently, given the above mentioned safety and efficacy results, the clinical relevance of the sponsor's claim that "clinical Study GF5503 has demonstrated that Serono's recombinant human FSH (Gonal-F) is as safe and effective as urinary FSH for the stimulation of follicular development" should be evaluated by the clinical reviewer.

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius 6-30-94

Dr. Dubey 6-30-94.

cc:
Orig. NDA 20-378
HFD-510
HFD-510/Dr. Sobel
HFD-510//Dr. Bennett
HFD-510/Ms. Galliers
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File 1.3.2 NDA]
HFD-713/Group 2 File
HFD-713/Mr. Marticello
Chron.

ajd/dm/wp5.2/NDA20-378/6-28-94

This review consists of 5 pages of text and 3 pages of tables.